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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/394,902	09/13/1999	Steven L. Stice	000270-026	5113

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EXAMINER	
TON, THAIAN N	
ART UNIT	PAPER NUMBER
1632	10

DATE MAILED: 12/06/2001

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/394,902	STICE ET AL.	
	Examiner	Art Unit	
	Thaian N. Ton	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the c rrespondence address --

Peri d for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-49* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☒ The oath or declaration is objected to by the Examiner.

Pri rity under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 1-49 are pending and under current examination.

Priority

The priority information in the first paragraph of the specification should be updated to state that Application US Serial No. 08/888,057 is now US Patent No. 6,235,969 and Application US Serial No. 08/781,752 is now US Patent No. 5,945,577.

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:

There is no signature of Steven L. Stice.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-5, 17-24, 29, 30, 32, 33, 34, 36, 37 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-26 of U. S. Patent No. 6,235,969 B1. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims are obvious over the claims of the '969 patent. The instant claims are to methods of cloning pigs and methods of cloning transgenic pigs. The claims of '969 are drawn to methods of cloning a pig and cloning a transgenic pig. Thus, the instant claims are obvious over the claims of the '969 patent as the ordinary artisan having claims 1-26 would have sufficient teachings and motivation to produce the cloned pigs as instantly claimed.

Claims 1-5, 11, 12-14, 17-24, and 29 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-18, 19, 21, 22 of U.S. Patent No. 5,945,577. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims are obvious over the '577 patent. The instant claims are to methods of cloning a pig and cloning a transgenic pig. The claims of '577 are drawn to methods of cloning mammals and methods of cloning transgenic mammals, with a specific claim to pig. Thus, the instant claims are obvious over the claims of the '577 patent as the ordinary artisan having claims 1-18, 19, 21, 22 would have sufficient teachings and motivation to produce the cloned pigs as instantly claimed.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-49 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of cloning a porcine fetus or live offspring by transfer of a differentiated pig cell or a pig cell nucleus into a pig oocyte, or an enucleated pig oocyte, to form a nuclear transfer unit, activating the nuclear transfer unit and transferring the cultured nuclear transfer unit into a female porcine, such that the nuclear transfer unit develops into a porcine fetus or live porcine and methods of producing a porcine CICM pluripotent cell line by nuclear transfer, the specification does not reasonably provide enablement for a method of cloning a porcine fetus or live offspring by nuclear transfer, and transfer the cultured nuclear transfer unit into any host mammal such that the nuclear transfer unit develops into a porcine fetus or animal. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claimed invention is directed to a method of cloning a porcine fetus or live offspring, comprising inserting a desired differentiated pig cell or cell nucleus into an optionally enucleated pig oocyte or blastomere under conditions suitable for the formation of a nuclear transfer unit, removing the endogenous nucleus from the oocyte or blastomere if not previously removed, activating the resulting nuclear transfer unit, optionally culturing the nuclear transfer unit, and transferring the cultured nuclear

transfer unit into a host mammal such that the nuclear transfer unit develops into a porcine fetus or animal. In further embodiments, the claimed invention is directed to methods of producing a porcine CICM pluripotent cell line.

The specification teaches methods for producing cloned pigs by nuclear transfer using differentiated cells, or nuclei derived from differentiated cells. The specification teaches methods for producing transgenic pigs as well as pluripotent pig CICM cells and cell lines (see pp. 8-9 of the instant specification). The specification teaches that the cells or tissues derived from the pig nuclear transfer units, fetuses or offspring can be used in the treatment or diagnosis of many diseases.

In particular, the specification teaches particular media that can be used for pig cloning (see pp. 44-46). The specification teaches a protocol for the aspiration of porcine ovarian follicles, the preparations of porcine follicular fluid, epidermal growth factor stock, chorionic gonatodotropin and human chorionic gonadotropin stock, db-cAMP, activation medium, and antibiotics (see pp. 48-49). The specification teaches the oocyte-cumulus complex collection and a preferred protocol for *in vivo* oocyte recovery and the transfer of NT pig embryos (see p. 51). The specification teaches the isolation of primary culture of porcine embryonic and adult fibroblast cells and the preparation of these cells for nuclear transfer (see pp. 51-52). After a maturation period, the cumulus cells removed from the collected oocytes which can then be enucleated. The cells are then electrofused and activated (see p. 55). The embryos are then transferred into recipient females, where fetuses can be collected, or the embryos can be developed to term to produce live offspring (see p. 58).

Some of the instant claims (1-40) encompass the implantation of cultured nuclear transfer units into surrogate mothers of different species. However, such implantation is not predictable, as Fehilly *et al.* (**Nature**, Vol. 307, 16 February 1984) teach that often two unrelated species cannot carry a live hybrid fetus to term due to factors such as interspecific pregnancies, placental abnormalities and maternal immunological reaction against foreign antigens of the conceptus which would be the cause of immediate abortion (see p. 634, 1st column, 2nd paragraph). Fehilly *et al.* summarize experiments for the production of such animals, and show an extremely low percentage of full term young (see Table 1, p. 635). Although Fehilly *et al.* show that is possible to produce embryos that have been implanted into surrogate mothers of a foreign species, it is clearly an unpredictable process.

Further, claims 1-40 are directed to the use of an enucleated blastomere as the recipient cell in the nuclear transfer. The specification discusses the use of oocytes as recipient cells for nuclear transfer (see pp. 25-27), however, the specification does not provide guidance or teaching with respect to the use of an enucleated blastomere in nuclear transfer. Furthermore, it has been found that nuclear transfer involving enucleated blastomeres is unpredictable and undeveloped. Kato *et al.* (Theriogenology, 37: 769-778, 1992) attempted to fuse mouse fetal germ cells with enucleated blastomeres of 2-cell embryos. Kato *et al.* used 3 groups of blastomeres, which were obtained at various time points. After fusion, the blastomeres were cultured to examine their developmental capacity (see Abstract). It was found that 2 of the 3 groups of fused blastomeres did not divide, but several from the third group divided (collected at 47-52 hours after treatment with human chorionic gonadotropin), and some developed into

normal blastocysts. These normal blastocysts were then transferred into recipient females and allowed to come to term. It was found that none of the resulting progeny showed any contribution of the donor germ cells. Kato *et al.* teach that the proportion of enucleated blastocysts that developed into normal blastocysts following nuclear transfer was quite low (see p. 777, 2nd paragraph) and state that, "Differences in developmental stages between germ cells and recipient two-cell embryos may have been too large to permit the production of chimeric offspring." (see p. 777, last paragraph). To this end, the use of enucleated blastomeres for nuclear transfer is unpredictable and undeveloped, and as such, it would have required undue experimentation one of skill in the art to use enucleated blastomeres for nuclear transfer with a reasonable expectation of success.

Furthermore, the claims are directed to the formation of a nuclear transfer unit. It is well-known in the nuclear transfer art that cell-cell fusion must take place in order to effect nuclear transfer; however, the claims do not provide such a step. To this end, the methods of cloning a porcine fetus or live offspring, as well as the method of producing porcine CICM cell lines would not be predicted to result in a successful nuclear transfer unit.

Accordingly, in view of the unpredictable state of the art for the implantation of embryos into surrogate mothers of foreign species, the unpredictable and undeveloped art of using enucleated blastomeres as recipient cells in nuclear transfer and the lack of guidance or working examples provided by the specification for use of enucleated blastomeres in nuclear transfer, as well as the requirement for cell-cell fusion to produce a successful nuclear transfer, it would have required undue experimentation for one

skilled in the art to make and/or use the claimed porcine fetuses or live offspring, cell lines, and methods of using the same.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 30-32, 36 and 41-48 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 30-32 recite the limitation "the fused nuclear transfer unit" in line 1 of the claims. There is insufficient antecedent basis for this limitation in the claims.

Claim 36 recites the limitation "the cloned NT unit" in lines 1-2. There is insufficient antecedent basis for this limitation in the claim.

Claim 41, as written is confusing. The claim recites the phrase, "CICM (pluripotent) cell line" in line 1 of the claim. It is unclear what the limitations of this phrase are. Clarification and/or amendment are requested. Claims 42-48 depend from claim 41.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 45 is rejected under 35 U.S.C. 102(a) as being anticipated by Wheeler (US Pat No. 5,523,226, published June 4, 1996).

The claim is directed to a transgenic CICM cell line, wherein the cell line has the identical genotype as a previously existing porcine differentiated cell that has been genetically modified. However, as claim 45 is a product-by-process claim, a teaching of the same product obtained by a different method serves as anticipatory art against the instant claim.

Wheeler teaches the isolation of inner cell mass (ICM) cells from a pig which can be cultured (see col. 7, lines 33-44). Wheeler teaches that these embryonic stem cells can be transformed with a nucleotide sequence (see col. 8, lines 21-27).

Accordingly, Wheeler anticipates claim 45.

Claims 35, 38-40 are rejected under 35 U.S.C. 102(b) as being anticipated by Fodor *et al.* (1994), PNAS, 91 11153-1157.

The claims are drawn to transgenic pig fetuses, offspring and progeny produced by the claimed methods of cloning a porcine fetus or porcine offspring. However, as claims 35, 38-40 are product-by-process claims, a teaching of the same products obtained by a different method serves as anticipatory art against the instant claims.

Fodor *et al.* teach the production of transgenic pigs which express a cDNA sequence encoding human CD59 (see p. 1115, Figure 2). The pigs disclosed by Fodor *et al.* are offspring and progeny of founder pigs (p. 11154, col. 1, 2nd paragraph, lines 2-4). As Fodor *et al.* teaches the injection of the transgene into pig embryos, pig fetuses are inherent in the development to term pigs. Claims 35, 38-40 do not distinguish transgenic fetuses, offspring, and progeny from the claimed fetuses from the fetuses, offspring and progeny taught by Fodor *et al.*

Accordingly, Fodor *et al.* anticipate claims 35, 38-40.

Claim 43 is rejected under 35 U.S.C. 102(b) as being anticipated by Strojek *et al.* (Theriogenology, 1990).

Claim 43 is directed to a CICM cell line which is pluripotent and comprises the same genotype as a previously existing non-embryonic differentiated cell. However, as claim 43 is a product-by-process claim, a teaching of the same product obtained by a different method serves as anticipatory art against the instant claim.

Strojek *et al.* teach the culture of ICM cells as cell lines (p. 903, 5th paragraph, lines 1-5, and p. 907, figure 2).

Accordingly, Strojek *et al.* anticipate claim 43.

Claim 48 rejected under 35 U.S.C. 102(b) as being anticipated by Chang *et al.* (Mol Biol Med, 1990, 7: 461-470).

Claim 48 is directed to differentiated cells. However, as claim 48 is a product-by-process claim, a teaching of the same product obtained by a different method serves as anticipatory art against the claim.

Chang *et al.* teach primary skin fibroblasts (see p. 462, 2nd column).

Accordingly, Chang *et al.* anticipate claim 48.

Conclusion

Claims 1-34, 36-37, 41, 42, 44, 46, 47, and 49 appear to be free of the cited prior art of record.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Thaian N. Ton whose telephone number is (703) 305-1019. The examiner can normally be reached on Monday through Friday from 8:00 to 5:00 (Eastern Standard Time), with alternating Fridays off. Should the examiner be unavailable, inquiries should be directed to Karen Hauda, Supervisory Primary Examiner of Art Unit 1632, at (703) 305-6608. Any administrative or procedural questions should be directed to Patsy Zimmerman, Patent Analyst, at (703) 305-2758. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 308-8724.

The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1632.

TNT

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